THE NEW ARMENIAN MEDICAL JOURNAL
Vol.7 (2013), No 4, p.42-47

INTRAOCULAR USE OF AVASTIN (BEVACIZUMAB) IN PATIENTS WITH NEOVASCULAR GLAUCOMA: EFFICACY AND SAFETY

Vardanyan A.H., Nasibyan N.L.*, Shahnazaryan H.G.

Ophthalmological Center after S.V. Malayan. Yerevan. Armenia

Received 1/23/2013; accepted in final form 10/28/2013

Abstract

Introduction: *Neovascular (hemorrhagic) glaucoma is one of the causes of irretrievable loss of vision throughout the world. The ischemic process in the retina brings to the formation of neovascular vessels in retina and iris as a result of vascular endothelial growth factor; this latter leads to a significant increase of intraocular pressure. Avastin (bevacizumab) neutralizes the vascular endothelial growth factor. Avastin is used intravitreously for treatment of ischemic diseases of the retina, such as diabetic retinopathy with macular edema, age-related macular degeneration with chorioneovascular membrane, as well as thrombosis of the central veins of the retina with macular edema.*

The aim of our work *was to reveal the efficacy and safety of avastin use in patients with secondary neovascular glaucoma.*

Material and Methods: *In 2008-2010 the investigation was done at the Ophthalmological Center after S.V. Malayan (Yerevan, Armenia) and embraced 29 eyes of 28 patients (14 women and 14 men) at the age of 30 to 86 years old (average age: 60.7). Among all studied patients, there were 26 subjects with diabetes mellitus and 2 patients applied after suffering thrombosis. All the patients had secondary neovascular glaucoma with different degree of rubeosis. The patients received antiglaucoma medical treatment. All the patients initially received 1.25 mg avastin injections: 18 eyes were injected in the anterior chamber and 11 eyes – intravitreously. The second injection of 1.25 mg avastin was given to 11 patients.*

Results and Discussion: *Improvement was noted in 25 of 29 eyes. By the end of the first month after avastin injection the increase of visual acuity, intraocular pressure normalization and absence of rubeosis were noted in 8 patients. In 11 patients improvement was also observed: reduction or normalization of intraocular pressure and decrease or absence of rubeosis; however, the visual acuity remained unchanged: 8 patients received avastin injection for the organ preservation purpose. Amongst 29 cases, in 28 rubeosis was absent or its degree decreased after the avastin injection; only in 1 patient the condition remained unchanged: the third degree rubeosis remained without worsening.*

Conclusion: *Taking into account the above mentioned, the authors have concluded that intraocular injection of avastin (1.25 mg) is an effective method for treatment of patients with secondary neovascular glaucoma. The procedure can be widely implemented in the clinical practice both independently and in combination with other treatment methods.*

Keywords: *secondary neovascular glaucoma, rubeosis, avastin.*

Introduction

All over the world, neovascular (hemorrhagic) glaucoma is one of the causes of irretrievable loss of vision. The ischemic process in the retina brings to formation of neovascular vessels in retina and iris as a result of vascular endothelial growth factor (VEGF); this latter leads to an expressed increase of intraocular pressure [*Adamis A. et al., 1994; Tripathi R. et al., 1998; Noma H. et al., 2005*]. Ischemia of the retina is mainly encountered in patients with diabetic retinopathy, thrombosis of the central retinal vein (CRV). Treatment of such patients is mainly surgical. Panretinal photolasercoagulation (PhLC) is also conducted to decrease vasoproliferative factor and probably cause regression of neovascularisation in the an-

Address for Correspondence:
Ophthalmological Center after S.V. Malayan
30 Fuchik Street, Yerevan, 0048, Republic of Armenia
Tel.: (374 91) 429 622
E-mail: n_nasibyan@yahoo.com

terior segment of the eye. Avastin (bevacizumab) inhibits binding of vascular endothelium receptors with the growth factor and is implemented for the treatment of metastatic colorectal cancer and some forms of other malignant tumors [*Cohen M. et al., 2007*].

Avastin is used intravitreously to treat ischemic diseases of the retina, such as diabetic retinopathy with macular edema, age-related maculodegereration with the presence of chorioneovascular membrane, thrombosis of CRV with macular edema [*Rich R. et al., 2006; Arevalo J. et al., 2007; Costa R. et al., 2007*]. The use of avastin injection in treatment of neovascular glaucoma was also described [*Davidorf F. et al., 2006; Kahook M. et al., 2006*].

Material and Methods

From 2008 to 2010, 29 eyes of 28 patients (14 women and 14 men) at the age of 30 to 86 years old (average age: 60.7) were investigated at the Ophthalmological Center after S.V. Malayan (Yerevan, Armenia). There were 26 patients with diabetes mellitus, 2 patients after suffering thrombosis. All the patients had secondary neovascular glaucoma with rubeosis of different degree. The patients received antiglaucoma medical treatment. Nine patients received panretinal PhLC before developing secondary neovascular glaucoma, 2 patients underwent panretinal PhLC during the first avastin injection. One patient, who had already had PhLC, received additional coagulants during the 1st avastin intravitreous injection, another patient underwent panretinal PhLC in a month after avastin intravitreous injection. The PhLC was done using the semiconductive diode laser "PURE-POINT" ("Alcon", USA).

Initially all the patients were injected 1.25 *mg* avastin ("Roche", Switzerland); 18 eyes were injected into the anterior chamber and 11 – intravitreously.

Among 18 patients with an injection into the anterior chamber, 7 patients received another injection of 1.25 *mg* avastin: 3 of them were given this injection again into the anterior chamber and 1 of them – twice; 4 patients got 1.25 *mg* avastin intravitreous injection: 2 of them twice additionally. Of 11 patients, who had intravitreous avastin injection, 4 patients were again injected 1.25 *mg* avastin: 3 of them intravitreously (one – three times, two of them – twice); 1 patient got another 1.25 *mg* avastin injection into the anterior chamber.

Before and after avastin injection, the visual acuity in investigated patients was determined in conventional units according to H. Snellen formula:

$$V = \frac{d}{D}$$

where V (Visus) is visual acuity; d – distance, at which the tested subject can see letters of the given row of the chart; D – distance, at which an eye with the normal visual acuity can see (in conventional units).

The intraocular pressure (IOP) was measured before and after avastin injection according to A. Maklakov and expressed as *mm Hg*.

The degree of rubeosis was evaluated in accordance with classification of Wand M. and coworkers (1978). The first degree rubeosis was assessed at presence of newly formed vessels along the pupillary edge of the iris, open anterior chamber angle; the second degree was recorded at newly formed vessels in all zones of the iris; the third degree was recorded at newly formed vessels in all zones of the iris, neovascularization of the anterir chamber angle, single zones of anterior chamber angle synechiae closure; the fourth degree was marked with newly formed vessels in all zones of the iris, anterior chamber angle closure [*Wand M. et al., 1978*].

Results and Discussion

The dynamics of visual acuity changes, as well as intraocular pressure and rubeosis degree before and after avastin injection is presented in % (Figures 1-3).

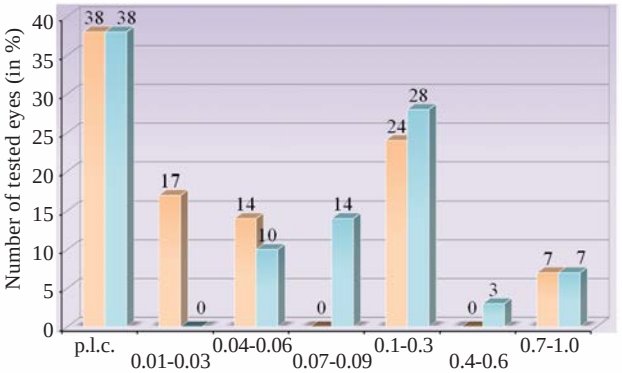

Figure 1. *Comparative characteristics of visual acuity averaged values in patients before (□) and after (□) avastin injection by the end of the 1st year of observation. Note: p.l.c. - proectia lucis certa.*

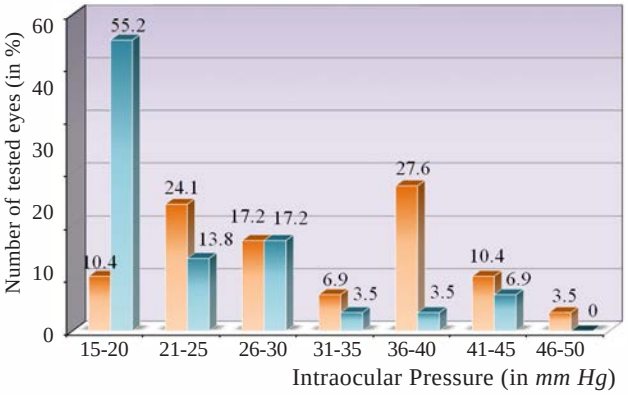

FIGURE 2. *Comparative characteristics of intraocular pressure averaged values in patients before (□) and after (□) avastin injection by the end of the 1st year of observation.*

The improvement was noted in 25 of 29 eyes. By the 1st month after avastin injection the improvement of visual acuity, IOP normalization and absence of rubeosis were noted in 8 patients. Among them in 5 patients the state remained unchanged during a year (2 of them underwent panretinal PhLC earlier, one of them got it during the injection). After the visual acuity improvement from 0.03 to 0.1 by the 2nd month one patient received another intravitreous avastin injection; the visual acuity increased up to 0.2. By the 3rd month after the 3rd injection visual acuity increased up to 0.3 and remained stable during 1 year. In the 2nd patient after the visual acuity increase from 0.1 to 0.3 a decrease of visual acuity up to 0.2 was noted in one and a half month. This patient received another intravitreous avastin injection, the visual acuity again increased up to 0.3, and his state remained unchanged during a year. In the latter of described cases (the patient after thrombosis) the visual acuity increased from 0.02 up to 0.1 after avastin injection into the anterior chamber, but by the 3rd month he developed the 1st degree rubeosis; the visual acuity was without any special changes – 0.09. The patient again received intravitreous avastin injection, after which rubeosis could not be noted biomicroscopically. The visual acuity increased up to 0.2, IOP remained at 17 *mm Hg*, by the year-end IOP became 19 *mm Hg*, rubeosis of the 2nd degree was recorded. The patient received intravitreous avastin injection once more (all the 3 patients had undergone panretinal PhLC previously).

In 1 patient visual acuity increase was noted from 0.05 to 0.08, as well as IOP decrease from 25 *mm Hg* to 20 *mm Hg*, the 2nd degree rubeosis turned into the 1st degree (the patient had undergone panretinal PhLC previously), but by the 8th month after the 1st avastin injection into the anterior chamber the patient's state worsened: visual acuity decreased up to 0.03, IOP made 25 *mm Hg*, the 1st degree rubeosis remained. The patient was again given intravitreous avastin injection, after which an improvement was noted anew: the visual acuity made 0.08, no rubeosis was biomicroscopically noted, IOP was at 20 *mm Hg* and the state remained stable during the year. By the 1st month after avastin injection into the anterior chamber the other patient's visual acuity increased from 0.04 to 0.1; his IOP decreased from 45 *mm Hg* to 23 *mm Hg* rubeosis of the 4th degree changed to the 2nd degree. The patient applied with pains; upon the pains relief, panretinal PhLC was conducted. However, by the 2nd month the patient noted deterioration: IOP increased up to 29 *mm Hg* visual acuity made 0.08, rubeosis was not biomicroscopically noted. The patient received another

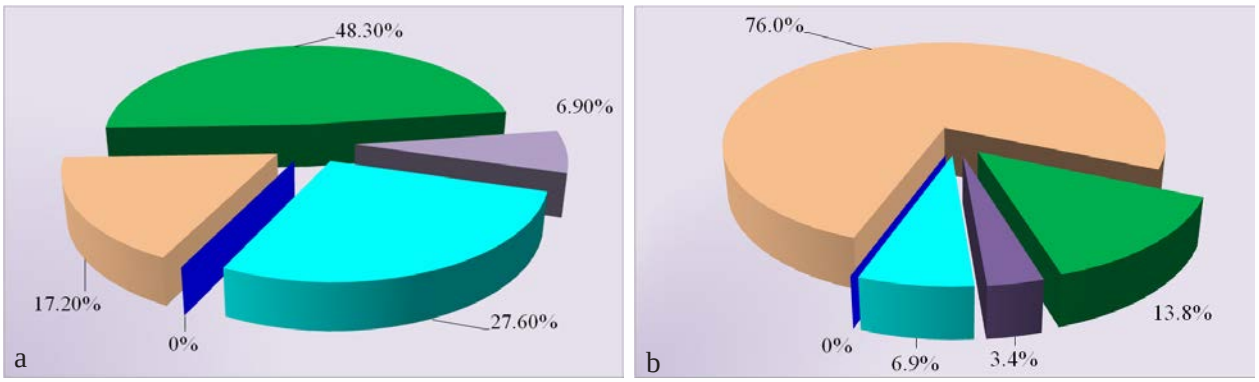

FIGURE 3. *Eyes distribution according to rubeosis degree before (**a**) and after (**b**) avastin injection (in %).*
-0 degree. -1st degree. -2nd degree. -3rd degree. -4th degree

intravitreous avastin injection, no changes were noted, and the patient was operated on.

Thus, only in 1 of the above mentioned patients deterioration of the overall state was noted by the end of the 1st year.

By the 1st month after the first avastin injection, the improvement was noted in 11 patients: decrease or normalization of IOP, decrease or absence of rubeosis, and unchanged visual acuity. Among the mentioned cases, 8 patients with the visual acuity of 0, *proectia lucis certa*, *proectia lucis incerta* received avastin injection to protect the organ. Six of them received avastin injection once: in 3 patients the injection was done into the anterior chamber, while 3 others were injected intravitreously. In 3 patients IOP normalized, rubeosis disappeared (1 patient had an acute attack that was coped), and the state remained stable during a year. In 2 patients IOP decreased from 34 *mm Hg* up to 28 *mm Hg* and from 38 *mm Hg* to 30 *mm Hg*, correspondingly; acute pains disappeared, the 3rd degree rubeosis turned into the 1st degree: the state was stable, no surgical intervention was needed. In another patient with acute attack the IOP decreased from 38 *mm Hg* to 28 *mm Hg* after the intravitreous injection, the attack was coped, rubeosis was absent (it was of the 3rd degree). By the 2nd month IOP normalized (18 *mm Hg*) without another avastin injection and remained stable by the year-end. In another patient, who also presented with an acute attack, the 1st avastin injection into the anterior chamber decreased IOP from 40 *mm Hg* to 19 *mm Hg*. the 3rd degree rubeosis was not noted biomicroscopically any more. the state was stable, and the attack coped. However, the patient decided to stop taking the administered antiglaucoma agents, and by the year-end he suffered pains in the eye, IOP made 38 *mm Hg*, rubeosis of the 3rd degree was observed. Avastin was injected into the anterior chamber of this patient, though without any improvement, pains did not disappear, the patient was suggested cidafarin injection, In another patient (with acute attacks) IOP decreased from 49 *mm Hg* to 41 *mm Hg*, the 4th degree rubeosis changed to the 3rd degree, the attack disappeared. However, by the 1st month IOP remained 41 *mm Hg*, another injection of avastin was given into the anterior chamber, rubeosis and pains disappeared, IOP remained unchanged at 41 *mm Hg*. By the 1st month after the injection, in 2 patients IOP became normal, rubeosis was not noted biomicroscopically, visual acuity remained unchanged: in one patient it was 0.1 (this patient got a single avastin injection into the anterior chamber with panretinal PhLC). in the second patient visual acuity made 1.0. A single intravitreous avastin injection was given, no PhLC was done, the patient previously suffered from CRV thrombosis. In both patients the state was stable during a year. In the latter patient IOP decreased from 38 *mm Hg* to 30 *mm Hg*, the 2nd degree rubeosis was not noted biomicroscopically, visual acuity after the 1st injection remained 0.2 (intravitreous avastin injection was given with panretinal PhLC). By the 1st month a second injection was performed into the anterior chamber, IOP made 26 *mm Hg*, no rubeosis was observed, visual acuity made 0.7, but by the 3rd month deterioration of the state was noted: visual acuity decreased to 0.06, IOP increased to 41 *mm Hg*, the 2nd degree rubeosis developed; the patient was not operated on.

Of these mentioned patients worsening of the state was noted in 2 patients; in 1 patient visual acuity decreased from 0.7 to 0.06 by the 5th month, and the patient was operated on. By the end of the 1st year after injection the second patient received avastin injection for organ protection purpose. Upon the first injection of avastin into the anterior chamber no rubeosis was noted in ether of the patients. and the state remained stable during a year (both patients received avastin injection for organ protection purpose). The IOP and vision acuity remained unchanged in both patients. Thus, the improvement could be noted in these 2 patients as well.

The improvement was also noted in the following 4 patients. In 1 patient IOP decreased from 38 *mm Hg* to 26 *mm Hg*, visual acuity increased from *proectia lucis certa* to 0.5, rubeosis changed from the 3rd to the 1st degree by the end of the 1st month, then by the 2nd month rubeosis disappeared without a second injection, IOP was 14 *mm Hg* and remained stable during a year (the injection was done into the anteriror chamber). In another patient IOP and visual acuity remained unchanged by the 1st month, rubeosis was not noted after the injection (avastin was injected into the anterior chamber); by the 2nd and the 3rd months repeated injections of avastin were performed, the

condition remained stable. In the third patient IOP decreased from 25 *mm Hg* to 22 *mm Hg*, rubeosis was absent (it was of the 1st degree); after intravitreous injection the visual acuity decreased from 0.7 to 0.6. However, by the 6th month, without a second injection, visual acuity of the patient increased up to 0.9 and remained stable during a year. In the 4th patient IOP decreased from 22 *mm Hg* to 20 *mm Hg*, the 1st degree rubeosis was not revealed biomicroscopically, visual acuity decreased from 0.1 to 0.09 remaining stable during a year without a second injection (earlier the patient underwent panretinal PhLC).

Deterioration was noted in 2 patients. In 1 patient after the 1st avastin injection into the anterior chamber the IOP increased from 30 *mm Hg* to 41 *mm Hg*, rubeosis disappeared; visual acuity remained unchanged at 0.02. By the 2nd month a second intravitreous avastin injection was administered, the visual acuity made 0.04, IOP was 38 *mm Hg*, no rubeosis was observed, and the surgical intervention was recommended. In the 2nd patient IOP increased from 22 *mm Hg* to 35 *mm Hg*, visual acuity decreased from 0.2 to 0.1, rubeosis was absent (it was of the 3rd degree). A second avastin injection was administered to this patient; by the 2nd month the 3rd degree rubeosis appeared, IOP was 35 *mm Hg*, pains subsided, and surgery was recommended (the patient underwent silicone oil removal).

In 28 of 29 eyes rubeosis was either absent or the degree reduced; only in 1 patient it remained unchanged, the 3rd degree rubeosis remained without deterioration.

Clinical case 1. Patient G.S., a 62-year-old male, Diagnosis: OS – secondary neovascular glaucoma. diabetic retinopathy. The patient applied to the clinic with complaints of pain in the left eye.

After the prior examination the visual acuity of the left eye was 0.01, IOP made 38 *mm Hg*, the 3rd degree rubeosis was observed. Avastin was injected intravitreously at 1.25 *mg* (Figure 4a). The patient did not claim to have any eye pains after the injection; the visual acuity increased to 0.1, while IOP decresed to 28 *mm Hg;* after the medical intervention the rubeosis decreased to the 2nd degree (Figure 4b). By the 1st month after injection the visual acuity was 0.1, IOP decreased to 24 *mm Hg*, no rubeosis was revealed biomicroscopically (Figure 4c).

Clinical case 2. Patient A.R., a 43-year-old female. Diagnosis: OS – secondary neovascular glaucoma, proliferative diabetic retinopathy. The patient underwent closed posterior vitrectomy on the left eye with silicone oil introduction and panretinal PhLC of the retina. After removal of silicone oil the secondary neovascular glaucoma developed. The visual acuity of the left eye was 0.1, IOP made 26 *mm Hg*, the 2nd degree rubeosis was observed. Avastin was injected into the anterior chamber at 1.25 *mg* (Figure 5a). On the 3rd day after avastin injection the visual acuity was 0.3, IOP decreased to 20 *mm Hg*, no rubeosis was observed biomicroscopically (Figure 5b).

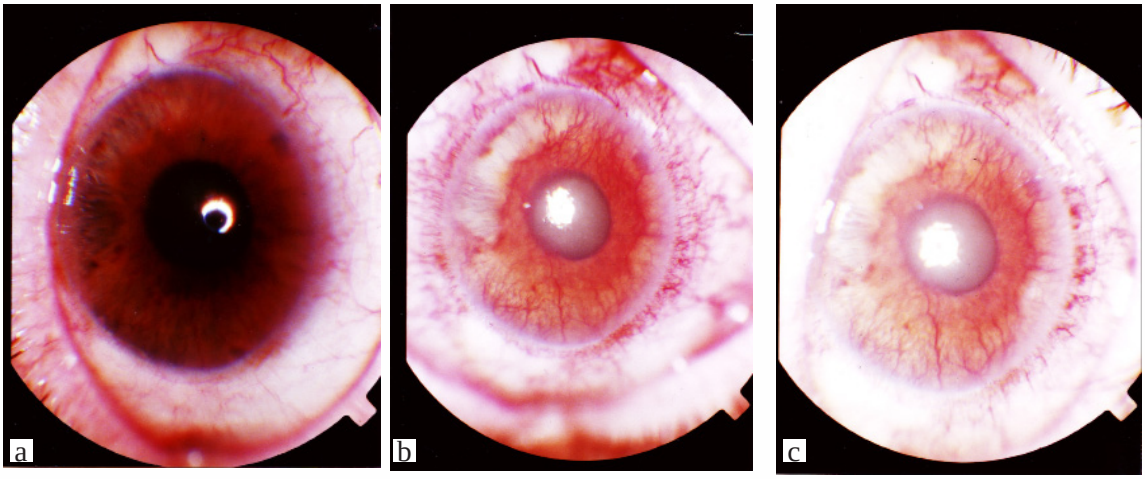

Figure 4. *Patient G.S. Anterior segment photograph of the eye before (a), in a day after (b) and by the end of the 1st month (c) after avastin injection.*

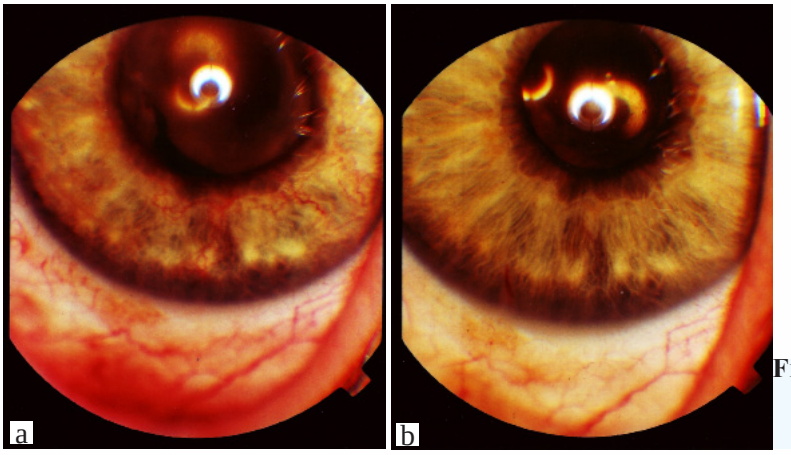

FIGURE 5. *Patient A.R. Photograph of the anterior segment of the eye before (a) and o in 3 days after (b) avastin injection.*

CONCLUSION

Avastin injection (1.25 *mg*) is an effective and safe method for treatment of patients with secondary neovascular glaucoma.

The use of 1.25 *mg* avastin dose level allows to significantly reduce the number of antiglaucoma surgeries (implanted Ahmed valve, etc.).

Avastin use decreases the number of post-surgical complications in secondary neovascular glaucoma, decreases the risk of hemorrhage.

Taking into account the above mentioned results. the authors concluded that intraocular injections of avastin (1.25 *mg*) present an effective method for management of patients with secondary neovascular glaucoma. The procedure can be recommended for wide implementation in clinical practice both independently and in combination with other methods of treatment.

REFERENCES

1. *Adamis A.P., Miller J.W., Bernal M.-T. et al.* Increased vascular, endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. Am. J. Ophthalmol. 1994; 118: 445-450.
2. *Arevalo J.F., Fromow-Guerra J., Quiroz-Mercado H. et al.* Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: results from the Pan-American Collaborative Retina study group at 6-month follow-up. Ophthalmology. 2007; 114: 743-750.
3. *Cohen M.H., Gootenberg J., Keegan P. et al.* FDA drug approval summary: bevacizumab (Avastin) plus carboplatin and paclitaxel as first-line treatment of advanced/metastatic recurrent nonsquamous non-small cell lung cancer. Oncologist. 2007; 12: 713-718.
4. *Costa R.A., Jorge R., Calucci D. et al.* Intravitreal bevacizumab (Avastin) for central and hemicentral retinal vein occlusions. IBeVO study. Retina. 2007; 27: 141-149.
5. *Davidorf F.H., Mouser J.G., Derick R.J.* Rapid improvement of rubeosis iridis from a single bevacizumab (Avastin) injection. Retina. 2006; 26: 354-356.
6. *Kahook M.Y., Schuman J.S., Noecker R.J.* Intravitreal bevacizumab in a patient with neovascular glaucoma. Ophthalmic Surg. Lasers Imaging. 2006; 37: 144-146.
7. *Noma H., Funatsu H., Yamasaki M. et al.* Pathogenesis of macular edema with branch retinal vein occlusion and intraocular levels of vascular endothelial growth factor and interleikin-6. Am. J. Ophthalmol. 2005; 140: 256-261.
8. *Rich R.M., Rosenfeld P.J., Puliafito C.A. et al.* Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Retina. 2006; 26: 495-511.
9. *Tripathi R.C., Li J., Tripathi B.J. et al.* Increased level of vascular endothelial growth factor in aqueous humor of patients with neovascular glaucoma. Opthalmology. 1998; 105: 232-237.
10. *Wand M, Dueker DK, Aiello LM, Grant WM.,* Effects of panretinal photocoagulation on rubeosis iridis, angle neovascularization, and neovascular glaucoma. Am. J. Ophthalmol. 1978 Sep; 86(3): 332-339.